II. REMARKS

Formal Matters

Claims 1-30, 32-34, 39, 48-50, 53-58, 61, 63, and 65 were previously cancelled without prejudice or disclaimer. Claims 40 and 64 have been withdrawn. Claims 31, 38, 41, 51, 52, and 60 have amended and claims 66-83 have been added. Upon entry of this amendment, claims 31, 35-38, 40-47, 51-52, 59-60, 62, 64, and 66-83 are under consideration.

The amendments to claims 31, 38, 41, 51, 52, and 60 were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. The amendments to claims 41, 51, and 52 are merely editorial in nature. Accordingly, no new matter is added by the amendments to claims 41, 51, and 52. Claims 31, 38, and 60 have been amended to recite "inhibitor of ErbB1 activation." Support for the amendments can be found throughout the specification, including at, e.g., p. 25-26, paragraphs [0079] – [0082]. Claim 31 has also been amended to recite "wherein the inhibitor of ErbB1 activation binds to ErbB1." Support for the amendment can be found throughout the specification, including at, e.g., p. 13, paragraph [0040]. Thus, the amendments are fully supported by the specification and do not add new matter.

New claims 66-83 are directed to a method of predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial response to treatment with an inhibitor of ErbB1 activation, wherein the inhibitor of ErbB1 activation is a monoclonal antibody that binds to ErbB1. Support for the claims can be found throughout the specification, for example, at p. 25, paragraph [0079]; p. 26, paragraphs [0081] and [0085]. Thus, the new claims are fully supported by the specification and do not add new matter.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Examiner Interview

The undersigned Applicants' representative thanks Examiner Amanda Shaw and Examiner Doug Schultz for the courtesy of an interview which took place on September 1, 2009, and which was attended by Examiners Shaw and Schultz, Dr. Joffre Baker (by telephone), Kathleen Determann (by telephone), and Applicants' representative Carol L. Francis (in person).

During the interview, the rejection under 35 U.S.C.§ 112, first paragraph, was discussed.

Claim objections

Claims 31 and 60 were objected to.

Claim 31 was objected to for having a typographical error. The Office Action stated that the word "and" should be deleted from the end of step (a). Accordingly, Applicants have amended claim 31 to delete the word "and" from the end of step (a).

The Office Action stated that claim 60 recites RNA transcripts that have not been elected.

Applicants note that there is no requirement to delete non-elected species from pending claims.

Therefore, Applicants respectfully request withdrawal of the objections.

Rejections under 35 U.S.C. §112, second paragraph

Claims 41-47, 51, and 59 were rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite.

Claims 41-47 and 59

The Office Action stated that there is insufficient antecedent basis for "the level of the LAMC2 RNA transcript in claim 41."

Claim 41 has been amended to recite "wherein the normalized level of the LAMC2 RNA transcript is determined . . . ."

Claim 51

The Office Action stated that there is insufficient antecedent basis for the phrase "said cooled lysis solution" in claim 51.

Claim 51 is amended to provide antecedent basis for "said cooled lysis solution."

Conclusion as to the rejections under 35 U.S.C. §112, second paragraph

Applicants submit that the above-discussed rejections under 35 U.S.C. §112, second paragraph, have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejections.

Rejection under 35 U.S.C. §112, first paragraph

Claims 31, 35-38, 41-47, 51, 52, 59, 60, and 62 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection.

In the amendment, filed on February 12, 2009, and responsive to the December 12, 2008, Office Action, Applicants provided arguments to rebut the "enablement" rejection. The extensive arguments filed on February 12, 2009, are not reiterated here. Nevertheless, as explained in the February 12, 2009, amendment, it is Applicants' position that the instant claims are in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph.

EGFR inhibitors

First, the Office Action stated that the Declaration of Joffre Baker (filed on December 21, 2006; "Baker Declaration") and the specification do not provide data "which separately establish the level of LAMC2 mRNA in subjects showing a beneficial response to erlotinib, subjects showing a beneficial response to cetuximab and subjects showing a beneficial response to gefitinib." Office Action, page 8. More specifically, the Office stated that "[i]n the absence of a clear showing of an association between increased LAMC2 mRNA levels and a clinically beneficial response to each of the drugs . . . it remains unpredictable as to whether LAMC2 mRNA levels can be used to predict the likelihood of a beneficial response to these drugs particularly since each of the claimed drugs is present in a different class of EGFR inhibitors and has a different mechanism in which it acts on the EGFR receptor." *Id.* Applicants respectfully disagree.

The instant claims now recite a "method for predicting the likelihood that a human colon cancer patient

will exhibit a clinically beneficial patient response to treatment with an inhibitor of ErbB1 activation . . . wherein the inhibitor of ErbB1 activation binds to ErbB1." The specification teaches that the EGFR family of growth factor receptors is "frequently **activated** in epithelial malignancies" and that EGFR is "known to be **active** in several tumor types, including . . . colon cancer . . . ." Specification at p. 25, paragraph [0079] (emphasis added). The specification further discloses that the "preferred inhibitors herein specifically interact with (e.g. bind to) an EGFR." Specification at p. 13, paragraph [0040]. The specification specifically discloses a class of EGFR inhibitors that inhibit ErbB1 activation by binding to ErbB1, including the tyrosine kinase inhibitors ZD1839 (also known as gefitinib or Iressa), LFM-A12, and OSI774 (also known as Erlotinib or Tarceva™); and the monoclonal antibody cetuximab. Specification at p. 25-26, paragraphs [0079]-[0082]. Consistent with the specification, independent claim 31 and its dependent claims specifically recite "wherein the inhibitor of ErbB1 activation . . . is erlotinib, cetuximab, or gefitinib." New independent claim 66 and its dependent claims specifically recite "wherein the inhibitor of ErbB1 activation is a monoclonal antibody that binds to ErbB1."

As way of background, activation of ErbB1 requires ligand binding to the extracellular domain of ErbB1 AND activation of the tyrosine kinase located at the intracellular domain of ErbB1. Upon activation of ErbB1, several tyrosine residues in the C-terminal domain of ErbB1 become autophosphorylated, which triggers downstream signaling by other proteins and initiates several signal transduction cascades, such as the MAPK, Akt and JNK pathways, leading to DNA synthesis and cell proliferation. As summarized by Baselga:

> The EGFR belongs to the erbB family of four closely related cell membrane receptors: EGFR (HER1 or erbB1), erbB2 (HER2), erbB3 (HER3), and erbB4 (HER4). These receptors are transmembrane glycoproteins that consist of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain with tyrosine kinase activity for signal transduction (Fig. 1). **Activation of the EGFR occurs when a ligand, such as epidermal growth factor (EGF), transforming growth factor-α (TGF-α), or amphiregulin, binds to its extracellular domain.** This causes the receptor to dimerize with either another EGFR monomer or with another member of the erbB family. **Following receptor dimerization, activation of the intrinsic protein tyrosine kinase activity and tyrosine autophosphorylation occur.** These events lead to the recruitment and phosphorylation of several intracellular substrates, leading to mitogenic signaling and other cellular activities.

Baselga, "Why the Epidermal Growth Factor Receptor: The Rationale for Cancer Therapy," The Oncologist

7(suppl 4):2-8 (Aug. 15, 2002) at p. 3, paragraph bridging left and right columns (emphasis added).

Baselga further explained that "receptor tyrosine kinase activity is required in cellular signaling." *Id.* at p. 3, right column, first paragraph. Thus, in general, initiation of the downstream signaling events first requires activation of EGFR via ligand binding and activation of tyrosine kinase.

The inhibitors of ErbB1 activation erlotinib, cetuximab, and gefitinib recited in independent claim 31, and a monoclonal antibody recited in independent claim 66, all have a common function in that they inhibit the very first step required for ErbB1-dependent cell signaling: activation of ErbB1 itself. As noted in previous responses and in the specification, for example, at page 26, paragraph [0081], cetuximab (also known as IMC-C225) is a monoclonal antibody that binds to the extracellular domain of ErbB1, thereby inhibiting the ligand binding step, which leads to inhibition of the tyrosine kinase. Erlotinib and gefitinib are both tyrosine kinase inhibitors that bind to ErbB1 and competitively inhibit the ATP binding site of EGFR. This class of ErbB1 inhibitors was well known before the November 15, 2002, priority date of the instant application and was known to inhibit the activation of ErbB1 and were considered to be the most promising. For example, Ciardiello and Tortora explained that:

> A large body of experimental and clinical work supports the view that the EGFR is a relevant target for cancer therapy. **Two therapeutic approaches have been shown most promising and are currently being used to inhibit EGFR in clinical studies: (a) MAbs [monoclonal antibodies]; and (b) small molecule inhibitors of the EGFR tyrosine kinase enzymatic activity**. MAbs are generally directed at the external domain of the EGFR to block ligand binding and receptor activation. TKIs [tyrosine kinase inhibitors] prevent the autophosphorylation of the intracellular tyrosine kinase domain of the EGFR.

Ciardiello and Tortora, "A Novel Approach in the Treatment of Cancer: Targeting the Epidermal Growth Factor Receptor," Clin. Cancer Res. 7:2958-2970 (Oct. 2001) at p. 2959, left column (emphasis added).

Ciardiello and Tortora further explained that monoclonal antibodies (MAbs) to EGFR "compete with these ligands [EGF and TGFα] for receptor binding, and block EGF- or TGFα-induced activation of EGFR tyrosine kinase." *Id.* At p. 2959, right column. Cetuximab (also known as IMC-C225) was also shown to "block EGF-induced autophosphorylation of the EFGR in cell lines *in vitro*." *Id.* Thus, inhibition of the ligand binding step leads to inhibition of the EGFR tyrosine kinase. While the tyrosine kinase inhibitors of ErbB1, such as

erlotinib and gefitinib, may allow ligand binding, they also inhibit activation of tyrosine kinase. Consequently, the MAbs and tyrosine kinase inhibitors of EGFR both function to inhibit activation of EGFR and lead to inhibition of the EGFR tyrosine kinase. Indeed, it has been shown that "[a]lthough IMC-C225 [the monoclonal antibody cetuximab] and the small molecule EGFR-TKI [EGFR tyrosine kinase inhibitor] have different mechanisms of action, they all ultimately lead to G_1 arrest via accumulations of $p27^{kip1}$." Ciardiello and Tortora, at p. 2966, left column, third full paragraph.

The Office cited to Giaccone as evidence that each ErbB1 inhibitor "has a different mechanism in which it acts on EGFR receptor" and thus, alleged it would be "highly unpredictable" to determine if "erlotinib, cetuximab, and gefitinib will each be less effective in patients with increased LAMC2 levels." Office Action at p. 8. However, Giaccone actually supports Applicants' position that erlotinib, cetuximab, and gefitinib fall within a class of ErbB1 inhibitors that have a common function and therefore, have predictable outcomes. Specifically, Giaccone reports that the response rates observed with gefitinib, erlotinib, and cetuximab appear similar in the same setting with non-small cell lung cancer (NSCLC):

> After failure of chemotherapy, **gefitinib and erlotinib** are able to induce major objective responses in approximately 10% of Caucasian patients and 25-30% of Japanese patients (gefitinib) with NSCLC tumors. **The response rate to the EGFR monoclonal antibody cetuximab . . . appears similar in the same setting**, but no experience is available in Asian patients.

Giaccone at p. 554, right column (emphasis added). Thus, Giaccone does not suggest that using erlotinib, cetuximab, and gefitinib will be "highly unpredictable" as the Office contends.

Others have also shown similar effects between these inhibitors of ErbB1 activation. For example, Albanell et al. showed that gefitinib (Iressa; ZD1839) and cetuximab (C225) were both able to inhibit activation of the major downstream signaling routes of EGFR, MAPKs ERK1 and ERK2 (ERK1/2), at drug concentrations that can be achieved in patients and that inhibit EGFR autophosphorylation in cultured cells. Albanell et al., "Activated Extracellular Signal-Regulated Kinases: Association with Epidermal Growth Factor Receptor/Transforming Growth Factor α Expression in Head and Neck Squamous Carcinoma and Inhibition by Anti-epidermal Growth Factor Receptor Treatments," *Cancer Research* 61:6500-6510 (2001) at p. 6508, col. 2,

last paragraph. Furthermore, when patients were treated with cetuximab (C225), they showed "markedly reduced levels of ERK1/2 activation in skin compared to skin from control patients." *Id.* at p. 6509, col. 1, first full paragraph. Patients treated with gefitinib (ZD1839) similarly "showed a significant decline in the expression of activated ERK1/2 in keratinocytes during therapy." *Id.*

Accordingly, while the Office appears to require data for each individual drug, there is no need to "separately establish the level of LAMC2 mRNA in subjects showing a beneficial response to erlotinib, subjects showing a beneficial response to cetuximab and subjects showing a beneficial response to gefitinib" because they are of the same class in that they all function to inhibit activation of ErbB1 by binding to ErbB1.

Nevertheless, the specification and the attached Declaration by Dr. Steve Shak adequately demonstrate that LAMC2 mRNA levels can be used to predict the likelihood of a beneficial response to inhibitors of ErbB1 activation that bind to ErbB1. Example 2 of the specification discloses the study of 23 colon adenocarcinoma patients treated with an EGFR inhibitor using a 192 gene assay. Specifically, mRNA was extracted from formalin-fixed colon tumor tissues obtained from each of the patients and molecular assays of quantitative gene expression on 192 genes were performed by RT-PCR. After removal of the colon tumor tissue, the patients were treated with an EGFR inhibitor and the patients were determined to have a partial response, stable disease, or progressive disease. The level of expression of mRNA transcripts in the colon tumors from each of the 23 patients was then correlated with either the partial response of the patients or the clinical benefit to the patients. Table 3 in the specification is a result of an analysis of all 23 patient samples compared to the three patients within that group that showed a partial response. Table 3 indicates that overexpression of LAMC2 in the colon tumor tissue showed a negative correlation with partial response to treatment with the EGFR inhibitors with a statistically significant p value of 0.0357.

In Dr. Steve Shak's declaration, Dr. Shak states that he inquired with co-inventor Dr. Jose Baselga, who had supervised or conducted the study with EGFR inhibitors on the 23 colon cancer patients described in Example 2 of the specification. Dr. Shak explains that he learned which EGFR inhibitor was used for each patient and that the EGFR inhibitors used to treat the 23 patients were EMD 72000 alone or cetuximab with or without

chemotherapy.[1] Specifically, 15 patients were treated with EMD 72000 alone and 8 patients were treated with cetuximab, either alone or with chemotherapy. Based on the information received for each specific patient, Dr. Shak determined that the three partial responders were treated with EMD 72000 alone. Dr. Shak also prepared a graph showing the LAMC2 mRNA level of each of the 23 patients, who were grouped into either non- partial responders ("No PR") or partial responders ("Yes PR"). *See* Exhibit B of Dr. Shak's declaration. As discussed above and in Dr. Shak's declaration and as shown in Table 3 of the specification, overexpression of LAMC2 in the colon tumor tissue showed a negative correlation with partial response to treatment with the EGFR inhibitors with a statistically significant p value of 0.0357. Thus, the data supports a "method for predicting the *likelihood* that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with an inhibitor of ErbB1 activation" by assaying a normalized level of the LAMC2 RNA transcript as recited in the claims.

Although the partial responders were all treated with EMD 72000, EMD 72000 is representative of monoclonal antibodies that bind to ErbB1 and inhibit the activation of ErbB1 by similar mechanisms as claimed in independent claim 66. As discussed above, cetuximab is a monoclonal antibody that specifically binds to ErbB1 and has been shown to be efficacious against EGFR-positive tumors. Like cetuximab, EMD 72000 was known before the earliest filing date of the instant application as a "monoclonal antibody that binds selectively to the EGFr and inhibits ligand mediated activation." Tewes et al., "Results of a Phase I Trial of the Humanized Anti Epidermal Growth Factor Receptor (EGFR) Monoclonal Antibody EMD 72000 in Patients With EGFR Expressing Solid Tumors," *Proc. Am. Soc. Clin. Oncol.* Abstract 378 (2002), presented at the 2002 American Society of Clinical Oncology (ASCO) Annual Meeting held in Orlando, Fla. From May 18-21, 2002 (see www.cancer.gov/asco2002/highlights). Also like cetuximab, "EMD 72000 showed a promising efficacy as single agent." *Id.* Because the monoclonal antibodies act by similar mechanisms by binding to ErbB1 and inhibit ErbB1 activation, it would not be unpredictable as to whether LAMC2 mRNA levels can be used to predict the

[1] Attached is also a Declaration of Joffre B. Baker, Ph.D., who attests that upon further information obtained by Dr. Steve Shak, the 23 colon adenocarcinoma patients described in Example 2 of the specification were treated with two of the five EGFR inhibitors previously identified in his declarations of December 21, 2006, and April 15, 2008: EMD 72000 or

likelihood of a beneficial response to monoclonal antibodies against ErbB1.

Moreover, results from monoclonal antibodies against ErbB1 can also be extrapolated to other inhibitors of ErbB1 that bind to ErbB1, such as Iressa (gefitinib) and Tarceva (erlotinib), which are recited in independent claim 31, because of their similar mechanisms of inhibition as discussed above. Significantly, the monoclonal antibody cetuximab showed similar response rates to other inhibitors of ErbB1 activation, Iressa (gefitinib) and Tarceva (erlotinib) when tested in the same setting. *See* Giaccone at p. 554, right column (quoted above); *see also* Albanell et al. discussed above. Therefore, the prognostic information obtained by overexpression of the LAMC2 gene as shown in Table 3 of the specification is applicable to treatment with the class of inhibitors of ErbB1 activation that bind to ErbB1, which includes Iressa (gefitinib), Tarceva (erlotinib), and cetuximab.

Accordingly, the specification, as evidenced by Dr. Steve Shak's declaration, fully enables a method for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with an inhibitor of ErbB1 activation that binds to ErbB1 and is erlotinib, cetuximab, or gefitinib (independent claim 31) or is a monoclonal antibody (independent claim 66) by assaying the normalized level of a LAMC2 transcript.

LAMC2 transcripts

Second, the Office stated that it is highly unpredictable if any LAMC2 transcript can be used to predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with an ErbB1 inhibitor. The Office stated that there are two LAMC2 transcripts, and that Airenne ((2000) *Cell Tissue Research* 300:129; "Airenne") supports the unpredictability.

However, the variant LAMC2 transcript is likely not present in colon cancer cells, and therefore not likely detected in a subject method as claimed. Airenne et al. ((1996) *Genomics* 32:54; "Airenne 1996") reported the structure of the human LAMC2 gene, noting the presence of two transcripts, denoted gamma 2 and gamma 2*. Airenne 1996 notes that while the longer gamma 2 chain transcript was strongly expressed in epithelia of all

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cetuximab.

tissues studied, the shorter gamma* chain mRNA was observed only in the cerebral cortex, in lung, and in distal tubules of the kidney. As such, Arienne does not support a conclusion that the instant claims lack enablement.

Conclusion as to the rejection under 35 U.S.C. §112, first paragraph

Applicants believe that claims 31, 35-38, 41-47, 51, 52, 59, 60, and 62 are fully enabled under 35 U.S.C. §112, first paragraph. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number GHDX-005.

Respectfully submitted,
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